

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207318Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NUPLAZID safely and effectively. See full prescribing information for NUPLAZID.

NUPLAZID™ (pimavanserin) tablets, for oral use
Initial U.S. Approval: 2016

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- ⚠ Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.
- ⚠ NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis. (5.1)

INDICATIONS AND USAGE

NUPLAZID is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. (1)

DOSAGE AND ADMINISTRATION

- Recommended dose is 34 mg, taken orally as two 17 mg tablets once daily, without titration. (2)
- Can be taken with or without food. (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 17 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- QT Interval Prolongation: Increases in QT interval; avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (≥5% and twice the rate of placebo): peripheral edema and confusional state. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ACADIA Pharmaceuticals Inc. at 1-844-422-2342 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inhibitors (e.g., ketoconazole): Reduce NUPLAZID dose by one-half. (2.2, 7.1)
- Strong CYP3A4 Inducers: Monitor for reduced efficacy. Increase in NUPLAZID dosage may be needed. (2.2, 7.1)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: No dosage adjustment for NUPLAZID is needed in patients with mild to moderate renal impairment. Use of NUPLAZID is not recommended in patients with severe renal impairment. (8.6)
- Hepatic Impairment: Use of NUPLAZID is not recommended in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2016

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FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis [see *Warnings and Precautions* (5.1)].

1 INDICATIONS AND USAGE

NUPLAZID™ is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis [see *Clinical Studies* (14)].

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The recommended dose of NUPLAZID is 34 mg, taken orally as two 17 mg strength tablets once daily, without titration.

NUPLAZID can be taken with or without food.

2.2 Dosage Modifications for Concomitant Use with CYP3A4 Inhibitors and Inducers

- Coadministration with Strong CYP3A4 Inhibitors

The recommended dose of NUPLAZID when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole) is 17 mg, taken orally as one tablet once daily [see *Drug Interactions* (7.1)].

- Coadministration with Strong CYP3A4 Inducers

Monitor patients for reduced efficacy if NUPLAZID is used concomitantly with strong CYP3A4 inducers; an increase in NUPLAZID dosage may be needed [see *Drug Interactions* (7.1)].

3 DOSAGE FORMS AND STRENGTHS

NUPLAZID (pimavanserin) is available as 17 mg strength tablets. The white to off-white, round, coated tablets are debossed on one side with a "P" and "17" on the reverse side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Antipsychotic drugs increase the all-cause risk of death in elderly patients with dementia-related psychosis. Analyses of 17 dementia-related psychosis placebo-controlled trials (modal duration of 10 weeks and largely in patients taking atypical antipsychotic drugs) revealed a risk of death in the drug-treated patients of between 1.6- to 1.7-times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. NUPLAZID is not approved for the treatment

of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis [see *Boxed Warning*].

5.2 QT Interval Prolongation

NUPLAZID prolongs the QT interval. The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin) [see *Drug Interactions* (7.1)]. NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval [see *Clinical Pharmacology* (12.2)].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis [see *Boxed Warning and Warnings and Precautions* (5.1)]
- QT Interval Prolongation [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical trial database for NUPLAZID consists of over 1200 subjects and patients exposed to one or more doses of NUPLAZID. Of these, 616 were patients with hallucinations and delusions associated with Parkinson's disease psychosis (PDP). In the placebo-controlled setting, the majority of experience in patients comes from studies evaluating once-daily NUPLAZID doses of 34 mg (N=202) compared to placebo (N=231) for up to 6 weeks. In the controlled trial setting, the study population was approximately 64% male and 91% Caucasian, and the mean age was about 71 years at study entry. Additional clinical trial experience in patients with hallucinations and delusions associated with PDP comes from two open-label, safety extension studies (total N=497). The majority of patients receiving long-term treatment received 34 mg once-daily (N=459). Over 300 patients have been treated for more than 6 months; over 270 have been treated for at least 12 months; and over 150 have been treated for at least 24 months.

The following adverse reactions are based on the 6-week, placebo-controlled studies in which NUPLAZID was administered once daily to patients with hallucinations and delusions associated with PDP.

Common Adverse Reactions (incidence $\geq 5\%$ and at least twice the rate of placebo): peripheral edema (7% NUPLAZID 34 mg vs. 2% placebo) and confusional state (6% NUPLAZID 34 mg vs. 3% placebo).

Adverse Reactions Leading to Discontinuation of Treatment

A total of 8% (16/202) of NUPLAZID 34 mg-treated patients and 4% (10/231) of placebo-treated patients discontinued because of adverse reactions. The adverse reactions that occurred in more than one patient and with an incidence at least twice that of placebo were hallucination (2% NUPLAZID vs. <1% placebo), urinary tract infection (1% NUPLAZID vs. <1% placebo), and fatigue (1% NUPLAZID vs. 0% placebo).

Adverse reactions that occurred in 6-week, placebo-controlled studies and that were reported at an incidence of $\geq 2\%$ and $>$ placebo are presented in **Table 1**.

Table 1 Adverse Reactions in Placebo-Controlled Studies of 6-Week Treatment Duration and Reported in $\geq 2\%$ and $>$ Placebo

Percentage of Patients Reporting Adverse Reaction		
	NUPLAZID 34 mg	Placebo
	N=202	N=231
Gastrointestinal disorders		
Nausea	7%	4%
Constipation	4%	3%
General disorders		
Peripheral edema	7%	2%
Gait disturbance	2%	$<1\%$
Psychiatric disorders		
Hallucination ^a	5%	3%
Confusional state	6%	3%

^a Hallucination includes visual, auditory, tactile, and somatic hallucinations.

Adverse Reactions in Demographic Subgroups

Examination of population subgroups in the 6-week, placebo-controlled studies did not reveal any differences in safety on the basis of age (≤ 75 vs. >75 years) or sex. Because the study population was predominantly Caucasian (91%; consistent with reported demographics for PD/PDP), racial or ethnic differences in the safety profile of NUPLAZID could not be assessed. In addition, in the 6-week, placebo-controlled studies, no clinically relevant differences in the incidence of adverse reactions were observed among those with a Mini-Mental State Examination (MMSE) score at entry of <25 versus those with scores ≥ 25 .

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with NUPLAZID

Table 2 Clinically Important Drug Interactions with NUPLAZID

QT Interval Prolongation	
Clinical Impact:	Concomitant use of drugs that prolong the QT interval may add to the QT effects of NUPLAZID and increase the risk of cardiac arrhythmia.
Intervention:	Avoid the use of NUPLAZID in combination with other drugs known to prolong QT interval [see <i>Warnings and Precautions</i> (5.2)].
Examples:	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide; Class 3 antiarrhythmics: amiodarone, sotalol; Antipsychotics: ziprasidone, chlorpromazine, thioridazine; Antibiotics: gatifloxacin, moxifloxacin
Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of NUPLAZID with a strong CYP3A4 inhibitor increases pimavanserin exposure [see <i>Clinical Pharmacology</i> (12.3)].
Intervention:	If NUPLAZID is used with a strong CYP3A4 inhibitor, reduce the dosage of NUPLAZID [see <i>Dosage and Administration</i> (2.2)].
Examples:	itraconazole, ketoconazole, clarithromycin, indinavir
Strong CYP3A4 Inducers	
Clinical Impact:	Concomitant use of a strong CYP3A4 inducer may reduce pimavanserin exposure resulting in a potential decrease in efficacy.
Intervention:	Patients should be monitored for reduced efficacy and an increase in dosage may be needed if NUPLAZID is used concomitantly with strong CYP3A4 inducers [see <i>Dosage and Administration</i> (2.2)].
Examples:	rifampin, carbamazepine, phenytoin, St. John's wort

7.2 Drugs Having No Clinically Important Interactions with NUPLAZID

Based on pharmacokinetic studies, no dosage adjustment of carbidopa/levodopa is required when administered concomitantly with NUPLAZID [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on NUPLAZID use in pregnant women that would allow assessment of the drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies, no adverse developmental effects were seen when pimavanserin was administered orally to rats or rabbits during the period of organogenesis at doses up to 10- or 12-times the maximum recommended human dose (MRHD) of 34 mg/day, respectively. Administration of pimavanserin to pregnant rats during pregnancy and lactation resulted in maternal toxicity and lower pup survival and body weight at doses which are 2-times the MRHD of 34 mg/day [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pimavanserin was not teratogenic in pregnant rats when administered during the period of organogenesis at oral doses of 0.9, 8.5, and 51 mg/kg/day, which are 0.2- and 10-times the maximum recommended human dose (MRHD) of 34 mg/day based on AUC at mid and high doses, respectively. Maternal toxicity included reduction in body weight and food consumption at the highest dose.

Administration of pimavanserin to pregnant rats during pregnancy and lactation at oral doses of 8.5, 26, and 51 mg/kg/day, which are 0.14- to 14-times the MRHD of 34 mg/day based on AUC, caused maternal toxicity, including mortality, clinical signs including dehydration, hunched posture, and rales, and decreases in body weight, and/or food consumption at doses ≥ 26 mg/kg/day (2-times the MRHD based on AUC). At these maternally toxic doses there was a decrease in pup survival, reduced litter size, and reduced pup weights, and food consumption. Pimavanserin had no effect on sexual maturation, neurobehavioral function including learning and memory, or reproductive function in the first generation pups up to 14-times the MHRD of 34 mg/day based on AUC.

Pimavanserin was not teratogenic in pregnant rabbits during the period of organogenesis at oral doses of 4.3, 43, and 85 mg/kg/day, which are 0.2- to 12-times the MHRD of 34 mg/day based on AUC. Maternal toxicity, including mortality, clinical signs of dyspnea and rales, decreases in body weight and/or food consumption, and abortions occurred at doses 12-times the MRHD of 34 mg/day based on AUC.

8.2 Lactation

Risk Summary

There is no information regarding the presence of pimavanserin in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUPLAZID and any potential adverse effects on the breastfed infant from NUPLAZID or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of NUPLAZID have not been established in pediatric patients.

8.5 Geriatric Use

No dose adjustment is required for elderly patients.

Parkinson's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of patients enrolled in the 6-week clinical studies with NUPLAZID [see *Adverse Reactions* (6.1)] was 71 years, with 49% 65-75 years old and 31% >75 years old. In the pooled population of patients enrolled in 6-week, placebo-controlled studies (N=614), 27% had MMSE scores from 21 to 24 compared to 73% with scores ≥ 25 . No clinically meaningful differences in safety or effectiveness were noted between these two groups.

8.6 Renal Impairment

No dosage adjustment for NUPLAZID is needed in patients with mild to moderate (CrCL ≥ 30 mL/min, Cockcroft-Gault) renal impairment [see *Clinical Pharmacology* (12.3)].

Use of NUPLAZID is not recommended in patients with severe renal impairment (CrCL < 30 mL/min, Cockcroft-Gault). NUPLAZID has not been evaluated in this patient population.

8.7 Hepatic Impairment

Use of NUPLAZID is not recommended in patients with hepatic impairment. NUPLAZID has not been evaluated in this patient population.

8.8 Other Specific Populations

No dosage adjustment is required based on patient's age, sex, ethnicity, or weight. These factors do not affect the pharmacokinetics of NUPLAZID [see *Clinical Pharmacology* (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

NUPLAZID is not a controlled substance.

9.2 Abuse

NUPLAZID has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence.

While short-term, placebo-controlled and long-term, open-label clinical trials did not reveal increases in drug-seeking behavior, the limited experience from the clinical trials do not predict the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed.

10 OVERDOSAGE

10.1 Human Experience

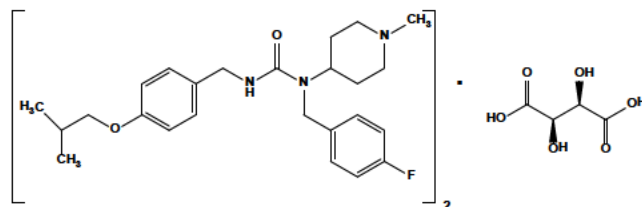
The pre-marketing clinical trials involving NUPLAZID in approximately 1200 subjects and patients do not provide information regarding symptoms with overdose. In healthy subject studies, dose-limiting nausea and vomiting were observed.

10.2 Management of Overdose

There are no known specific antidotes for NUPLAZID. In managing overdose, cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias [see *Warnings and Precautions* (5.2)]. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of NUPLAZID [see *Drug Interactions* (7.1)]. Consider the long plasma half-life of pimavanserin (about 57 hours) and the possibility of multiple drug involvement. Consult a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice.

11 DESCRIPTION

NUPLAZID contains pimavanserin, an atypical antipsychotic, which is present as pimavanserin tartrate salt with the chemical name, urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidiny)-*N'*-[[4-(2-methylpropoxy)phenyl]methyl]-, (2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1). Pimavanserin tartrate is freely soluble in water. Its molecular formula is $(C_{25}H_{34}FN_3O_2)_2 \cdot C_4H_6O_6$ and its molecular weight is 1005.20 (tartrate salt). The chemical structure is:



The molecular formula of pimavanserin free base is $C_{25}H_{34}FN_3O_2$ and its molecular weight is 427.55.

NUPLAZID tablets are intended for oral administration only. Each round, white to off-white, immediate-release, film-coated tablet contains 20 mg of pimavanserin tartrate, which is equivalent to 17 mg of

pimavanserin free base. Inactive ingredients include pregelatinized starch, magnesium stearate, and microcrystalline cellulose. Additionally, the following inactive ingredients are present as components of the film coat: hypromellose, talc, titanium dioxide, polyethylene glycol, and saccharin sodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of pimavanserin in the treatment of hallucinations and delusions associated with Parkinson's disease psychosis is unknown. However, the effect of pimavanserin could be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors and to a lesser extent at serotonin 5-HT_{2C} receptors.

12.2 Pharmacodynamics

In vitro, pimavanserin acts as an inverse agonist and antagonist at serotonin 5-HT_{2A} receptors with high binding affinity (K_i value 0.087 nM) and at serotonin 5-HT_{2C} receptors with lower binding affinity (K_i value 0.44 nM). Pimavanserin shows low binding to sigma 1 receptors (K_i value 120 nM) and has no appreciable affinity (K_i value >300 nM), to serotonin 5-HT_{2B}, dopaminergic (including D₂), muscarinic, histaminergic, or adrenergic receptors, or to calcium channels.

Cardiac Electrophysiology

The effect of NUPLAZID on the QTc interval was evaluated in a randomized placebo- and positive-controlled double-blind, multiple-dose parallel thorough QTc study in 252 healthy subjects. A central tendency analysis of the QTc data at steady-state demonstrated that the maximum mean change from baseline (upper bound of the two-sided 90% CI) was 13.5 (16.6) msec at a dose of twice the therapeutic dose. A pharmacokinetic/pharmacodynamic analysis with NUPLAZID suggested a concentration-dependent QTc interval prolongation in the therapeutic range.

In the 6-week, placebo-controlled effectiveness studies, mean increases in QTc interval of ~5-8 msec were observed in patients receiving once-daily doses of NUPLAZID 34 mg. These data are consistent with the profile observed in a thorough QT study in healthy subjects. Sporadic QTcF values ≥ 500 msec and change from baseline values ≥ 60 msec were observed in subjects treated with NUPLAZID 34 mg; although the incidence was generally similar for NUPLAZID and placebo groups. There were no reports of torsade de pointes or any differences from placebo in the incidence of other adverse reactions associated with delayed ventricular repolarization in studies of NUPLAZID, including those patients with hallucinations and delusions associated with PDP [see *Warnings and Precautions* (5.2)].

12.3 Pharmacokinetics

Pimavanserin demonstrates dose-proportional pharmacokinetics after single oral doses from 17 to 255 mg (0.5- to 7.5-times the recommended dosage). The pharmacokinetics of pimavanserin are similar in both the study population and healthy subjects. The mean plasma half-lives for pimavanserin and the active metabolite (*N*-desmethylated metabolite) are approximately 57 hours and 200 hours, respectively.

Absorption

The median T_{max} of pimavanserin was 6 (range 4-24) hours and was generally unaffected by dose. The bioavailability of pimavanserin oral tablet and pimavanserin solution was essentially identical. The formation of the major circulating *N*-desmethylated metabolite AC-279 (active) from pimavanserin occurs with a median T_{max} of 6 hours.

Ingestion of a high-fat meal had no significant effect on rate (C_{max}) and extent (AUC) of pimavanserin exposure. C_{max} decreased by about 9% while AUC increased by about 8% with a high-fat meal.

Distribution

Pimavanserin is highly protein bound (~95%) in human plasma. Protein binding appeared to be dose-independent and did not change significantly over dosing time from Day 1 to Day 14. Following administration of a single dose of NUPLAZID (34 mg), the mean (SD) apparent volume of distribution was 2173 (307) L.

Elimination

Metabolism

Pimavanserin is predominantly metabolized by CYP3A4 and CYP3A5 and to a lesser extent by CYP2J2, CYP2D6, and various other CYP and FMO enzymes. CYP3A4 is the major enzyme responsible for the formation of its major active metabolite (AC-279). Pimavanserin does not cause clinically significant CYP inhibition or induction of CYP3A4. Based on *in vitro* data, pimavanserin is not an irreversible inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4).

Based on *in vitro* studies, transporters play no significant role in the disposition of pimavanserin.

AC-279 is neither a reversible or irreversible (metabolism-dependent) inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). AC-279 does not cause clinically significant CYP3A induction and is not predicted to cause induction of any other CYP enzymes involved in drug metabolism.

Excretion

Approximately 0.55% of the 34 mg oral dose of ¹⁴C-pimavanserin was eliminated as unchanged drug in urine and 1.53% was eliminated in feces after 10 days.

Less than 1% of the administered dose of pimavanserin and its active metabolite AC-279 were recovered in urine.

Specific Populations

Population PK analysis indicated that exposure of pimavanserin in patients with mild to moderate renal impairment was similar to exposure in patients with normal renal function. Age, sex, ethnicity, and weight do not have clinically relevant effect on the pharmacokinetics of pimavanserin.

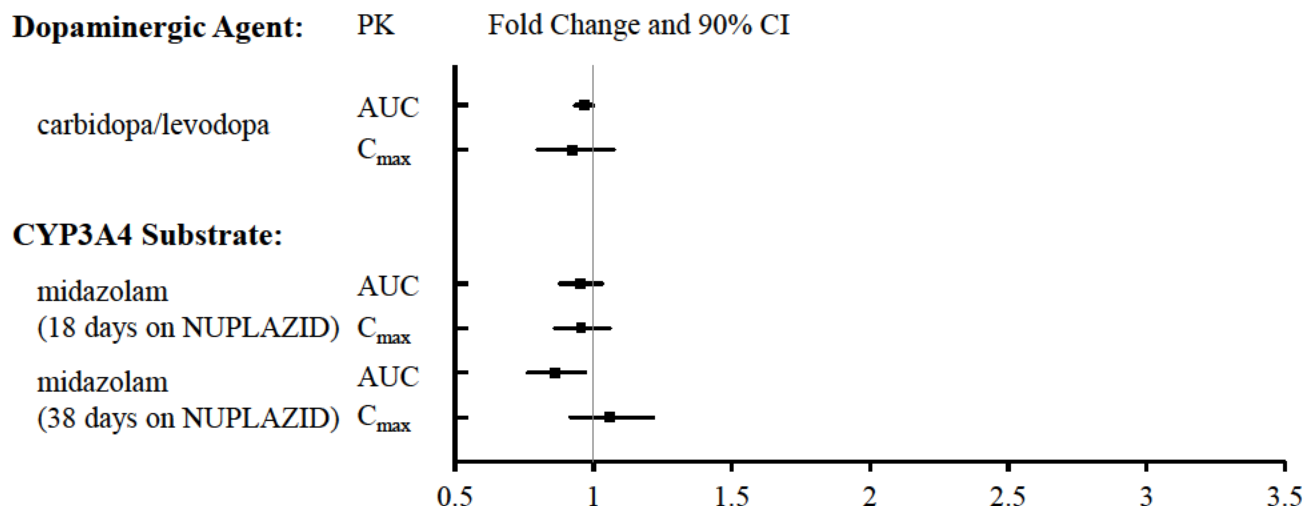
Pimavanserin has not been studied in patients with severe renal impairment or mild to severe hepatic impairment [see *Use in Specific Populations* (8.6, 8.7)].

Drug Interaction Studies

CYP3A4 Inhibitor: ketoconazole, a strong inhibitor of CYP3A4, increased pimavanserin C_{max} by 1.5-fold and AUC by 3-fold [see *Dosage and Administration* (2.2) and *Drug Interactions* (7.1)].

The effect of pimavanserin on other drugs is shown in **Figure 1**.

Figure 1 The Effects of Pimavanserin on the Pharmacokinetics of Other Drugs



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There was no increase in the incidence of tumors following daily oral administration of pimavanserin to mice or rats for 2 years. Mice were administered pimavanserin at oral doses of 2.6, 6, and 13 (males)/8.5, 21, and 43 mg/kg/day (females) which are 0.01- to 1- (males)/0.5- to 7- (females) times the MRHD of 34 mg/day based on AUC. Rats were administered pimavanserin at oral doses of 2.6, 8.5, and 26 (males)/4.3, 13, and 43 mg/kg/day (females) which are 0.01- to 4- (males)/0.04- to 16- (females) times the MRHD of 34 mg/day based on AUC.

Mutagenesis

Pimavanserin was not mutagenic in the *in vitro* Ames reverse mutation test, or in the *in vitro* mouse lymphoma assay, and was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

Pimavanserin was administered orally to male and female rats before mating, through mating, and up to Day 7 of gestation at doses of 8.5, 51, and 77 mg/kg/day, which are approximately 2-, 15-, and 22-times the maximum recommended human dose (MRHD) of 34 mg/day based on mg/m², respectively. Pimavanserin had no effect on fertility or reproductive performance in male and female rats at doses up to 22-times the MRHD of 34 mg based on mg/m². Changes in uterine parameters (decreases in the number of corpora lutea, number of implants, viable implants, and increases in pre-implantation loss, early resorptions and post-implantation loss) occurred at the highest dose which was also a maternally toxic dose. Changes in sperm parameters (decreased density and motility) and microscopic findings of cytoplasmic vacuolation in the epididymis occurred at doses approximately 15-times the MRHD of 34 mg/day based on mg/m².

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (foamy macrophages and/or cytoplasmic vacuolation) was observed in multiple tissues and organs of mice, rats, and monkeys as early as 14 days following oral daily administration of pimavanserin. The most severely affected organs were the lungs and kidneys. The occurrence of phospholipidosis was both dose- and duration-dependent. Diffuse phospholipidosis with focal/multifocal chronic inflammation was

observed in the lungs of rats treated for ≥ 3 months at doses ≥ 10 -times the maximum recommended human dose (MRHD) of 34 mg/day based on AUC. As a result of chronic inflammation, inflammatory lung fibrosis was observed in rats treated for 3 and 6 months at doses ≥ 18 -times the MRHD of 34 mg/day based on AUC. The findings in the lungs correlated with increased lung weights (up to 3-times those of controls) and respiratory-related clinical signs including rales, labored breathing, and gasping. Phospholipidosis in lungs of rats caused mortality at doses ≥ 16 -times the MRHD of 34 mg/day based on AUC. The estimated No Observed Effect Level (NOEL) for chronic lung inflammation in rats is 5-fold the MRHD of 34 mg/day based on AUC. Phospholipidosis was associated with increased kidney weights and tubular degeneration in rats at doses ≥ 10 -times the MRHD of 34 mg/day based on AUC. The relevance of these findings to human risk is not known.

14 CLINICAL STUDIES

The efficacy of NUPLAZID 34 mg as a treatment of hallucinations and delusions associated with Parkinson's disease psychosis was demonstrated in a 6-week, randomized, placebo-controlled, parallel-group study. In this outpatient study, 199 patients were randomized in a 1:1 ratio to NUPLAZID 34 mg or placebo once daily. Study patients (male or female and aged 40 years or older) had a diagnosis of Parkinson's disease (PD) established at least 1 year prior to study entry and had psychotic symptoms (hallucinations and/or delusions) that started after the PD diagnosis and that were severe and frequent enough to warrant treatment with an antipsychotic. At entry, patients were required to have a Mini-Mental State Examination (MMSE) score ≥ 21 and to be able to self-report symptoms. The majority of patients were on PD medications at entry; these medications were required to be stable for at least 30 days prior to study start and throughout the study period.

The PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) was used to evaluate the efficacy of NUPLAZID 34 mg. SAPS-PD is a 9-item scale adapted for PD from the Hallucinations and Delusions domains of the SAPS. Each item is scored on a scale of 0-5, with 0 being none and 5 representing severe and frequent symptoms. Therefore, the SAPS-PD total score can range from 0 to 45 with higher scores reflecting greater severity of illness. A negative change in score indicates improvement. Primary efficacy was evaluated based on change from baseline to Week 6 in SAPS-PD total score.

As shown in **Table 3**, **Figure 2**, and **Figure 3**, NUPLAZID 34 mg (n=95) was statistically significantly superior to placebo (n=90) in decreasing the frequency and/or severity of hallucinations and delusions in patients with PDP as measured by central, independent, and blinded raters using the SAPS-PD scale. An effect was seen on both the hallucinations and delusions components of the SAPS-PD.

Table 3 Primary Efficacy Analysis Result Based on SAPS-PD (N=185)

Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference ^a (95% CI)
SAPS-PD	NUPLAZID	15.9 (6.12)	-5.79 (0.66)	-3.06* (-4.91, -1.20)
	Placebo	14.7 (5.55)	-2.73 (0.67)	--
SAPS-PD Hallucinations ^b	NUPLAZID	11.1 (4.58)	-3.81 (0.46)	-2.01 (-3.29, -0.72)
	Placebo	10.0 (3.80)	-1.80 (0.46)	--
SAPS-PD Delusions ^b	NUPLAZID	4.8 (3.59)	-1.95 (0.32)	-0.94 (-1.83, -0.04)
	Placebo	4.8 (3.82)	-1.01 (0.32)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

^a Difference (drug minus placebo) in least-squares mean change from baseline.

^b Supportive analysis.

* Statistically significantly superior to placebo.

The effect of NUPLAZID on SAPS-PD improved through the six-week trial period, as shown in **Figure 2**.

Figure 2 SAPS-PD Change from Baseline through 6 Weeks Total Study Treatment

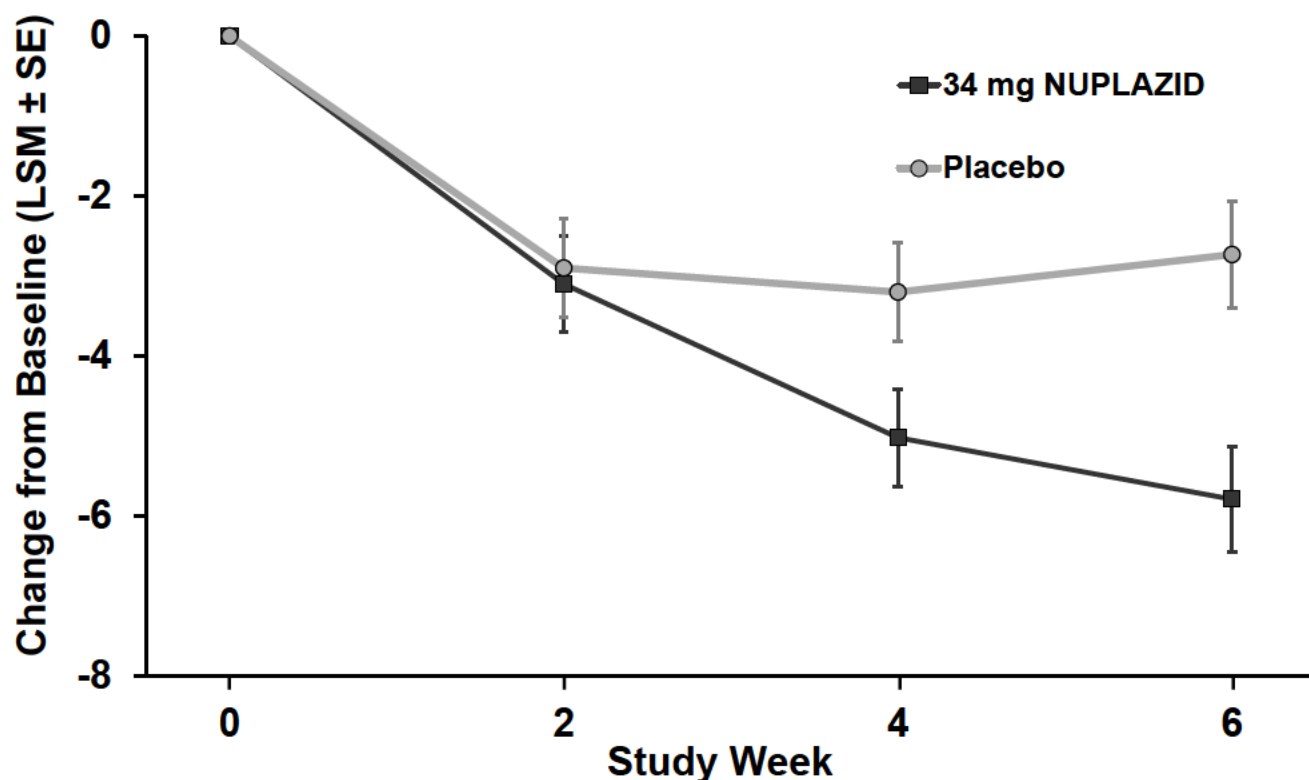
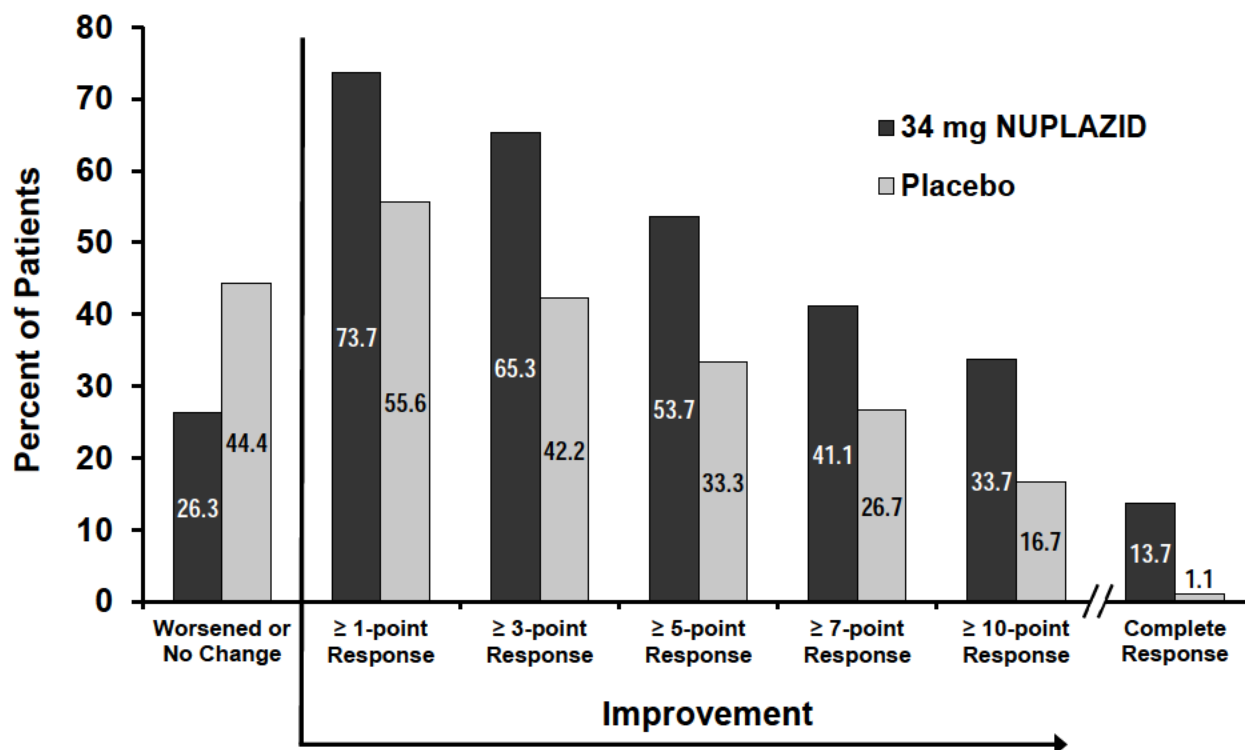


Figure 3 Proportion of Patients with SAPS-PD Score Improvement at the End of Week 6 (N=185)

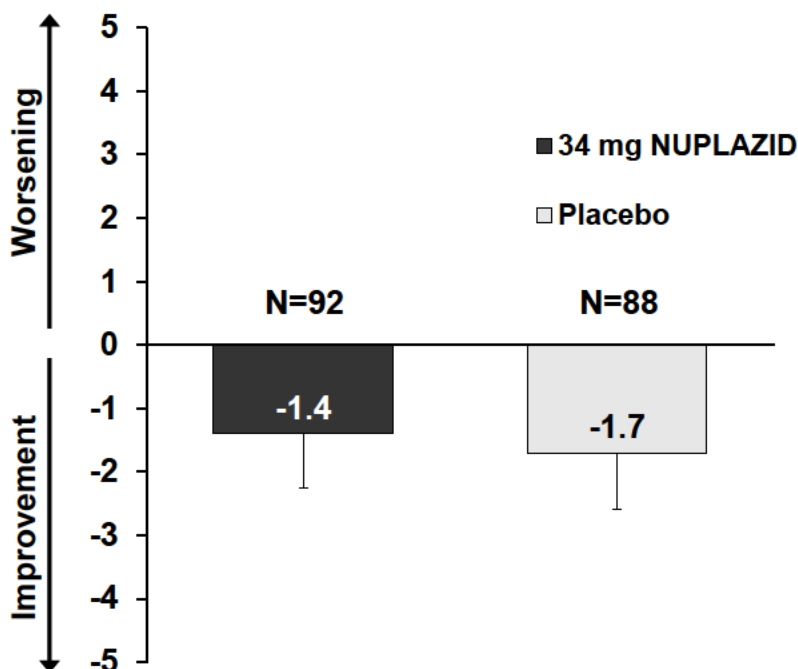


Complete response = SAPS-PD score reduced to zero from baseline value.
Patients with missing values were counted as non-responders.

Motor Function in Patients with Hallucinations and Delusions Associated with Parkinson's Disease Psychosis

NUPLAZID 34 mg did not show an effect compared to placebo on motor function, as measured using the Unified Parkinson's Disease Rating Scale Parts II and III (UPDRS Parts II+III) (**Figure 4**). A negative change in score indicates improvement. The UPDRS Parts II+III was used to assess the patient's Parkinson's disease state during the 6-week double-blind treatment period. The UPDRS score was calculated as the sum of the 40 items from activities of daily living and motor examination, with a range of 0 to 160.

Figure 4 Motor Function Change from Baseline to Week 6 in UPDRS Parts II+III (LSM - SE)



LSM: least-squares mean; SE: standard error. The error bars extend one SE below the LSM.

16 HOW SUPPLIED/STORAGE AND HANDLING

NUPLAZID (pimavanserin) tablets are available as:

17 mg Tablet:

White to off-white, round, coated tablet debossed with "P" on one side and "17" on the reverse.

Bottle of 60: NDC 63090-170-60

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

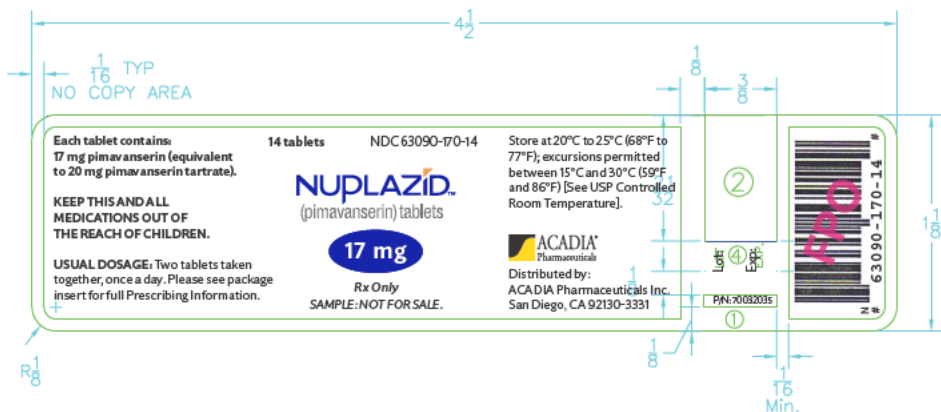
17 PATIENT COUNSELING INFORMATION

Concomitant Medication

Advise patients to inform their healthcare providers if there are any changes to their current prescription or over-the-counter medications, since there is a potential for drug interactions [see *Warnings and Precautions (5.2)*, *Drug Interactions (7)*].

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NUPLAZID™
(pimavanserin) tablets

14 tablets NDC 63090-170-14

NUPLAZID™
(pimavanserin) tablets

17 mg

Rx only

Rx only NDC 63090-170-14

Each tablet contains:
17 mg pimavanserin (equivalent to
20 mg pimavanserin tartrate).

USUAL DOSAGE: Two tablets taken
together, once a day. Please see
package insert for full Prescribing
Information.

Store at 20°C to 25°C (68°F to 77°F);
excursions permitted between 15°C
and 30°C (59°F and 86°F) [See USP
Controlled Room Temperature].

SAMPLE: NOT FOR SALE.



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ROBERT TEMPLE
04/29/2016